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Research article

Risk of adverse outcomes following treatment with direct acting antiviral drugs in HCV infected patients with liver cirrhosis

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ABSTRACT

Introduction: Hepatitis C virus (HCV) is the second major cause of death in Pakistan. Previously, interferon-based regimens were considered highly recommended therapy for HCV patients. Since 2015, interferon-based therapy has been replaced with interferon-free therapy also known as Direct Acting Antiviral (DAA) drugs. The treatment response of interferon-free regimens has been reported as highly effective treatment option with more than 90% sustained virological response (SVR) in chronic HCV infected patients in western countries of the world.

Objective: This study aims to analyze the treatment response of DAA drugs in HCV-infected Pakistani population with liver cirrhosis.

Methodology: We collected the total 94 sample of the HCV infected patients, from June 2020 to September 2020. Forty-six (46) patients were cirrhotic, and forty-eight (48) patients were non-cirrhotic. Data was analyzed using IBM SPSS version 21 software.

Conclusion: The findings of our study suggest that the response rate was 82.60% in HCV cirrhotic patients and 68.75% in HCV non-cirrhotic patients. Our study showed that overall treatment response was independent of age and gender. We also observed some adverse effects such as hepatocellular carcinoma, portosystemic encephalopathy (PSE), spontaneous bacterial peritonitis (SBP), hepatorenal syndrome (HRS), upper gastrointestinal bleeding (UGIB), ascites, among patients following treatment with interferon-free regimens.

1. Introduction

Hepatitis C virus (HCV) was firstly diagnosed in 1989 [1]. HCV is a life-threatening pathogen and a worldwide health problem. It is a major cause of morbidity and mortality [2]. The high risk of HCV leads to life-threatening complications such as chronic liver disease (CLD), hepatic failure, fibrosis, hepatocellular carcinoma (HCC), liver cirrhosis and end-stage liver disease [3]. HCV is an RNA virus and it belongs to the *Flaviviridae* family. HCV is a blood-borne pathogen that cause chronic HCV infection. The chronic HCV infection is

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present in 55%–85% of HCV infected patients [3]. Cirrhosis is the terminal stage of HCV infection. Direct Acting Antiviral (DAA) drug is prescribed to both cirrhotic and non-cirrhotic patients infected with HCV. Interferon based therapy was considered the standard care of therapy in the past until 2013 but interferon therapy showed lower efficacy and tolerability in both cirrhotic and non-cirrhotic patients. Development of hepatocellular carcinoma (HCC) and end stage liver disease (ESLD) increases day by day due to the initial risk of cirrhosis [4]. Inflammation, fibrosis, cirrhosis and ESLD are the stages of the chronic liver disease. The mortality rate increases due to cirrhosis and HCC also, HCC is the most common cancer related to death in Pakistan [5].

DAA drugs are considered the highly recommended therapy for chronic HCV patients because of its efficacy and tolerability as compared to interferon (INF) treated patients. Real world clinical experience showed that the greater number of HCV cirrhotic patients, transplantation recipients, and critical treated patients has cleared HCV infection by the treatment with the second generation of DAAs drugs. The duration of the treatment with DAA drugs is between 12 and 24 weeks based on the conditions of patient's liver [6]. Treatment response is estimated as SVR 12 and SVR 24 given that HCV RNA not detected via PCR, after completion of DAA drug therapy. The DAA drugs reduce the rate of relapse, reinfection, and liver cirrhosis [7].

The research reported 94.6% SVR following DAA drug therapy and the response rate of DAA drug was found to be more effective than interferon therapy. The study confirmed high end treatment response (ETR) (aviremic state after 1 month of completion of treatment) as well as SVR (aviremic state after 1 year of completion of treatment) in patients treated with DAA drugs [8].

Some existing evidence from literature reported DAA drug induced hepatotoxicity [9,10] therefore, it is necessary to monitor patients' post-treatment to detect the liver associated complications at early stages.

The aim of this study is to determine the efficacy of direct acting antiviral drugs in cirrhotic and non-cirrhotic HCV patients. Our purpose is to find out the outcomes of DAAs in the patients with compensated & decompensated cirrhosis and HCC.

2. Methodology

2.1. Study design

We conducted longitudinal retrospective cohort study recruiting participants treated with direct acting antiviral (DAA) drugs. There were two treatment groups: HCV patients with liver cirrhosis and HCV patients with non-cirrhotic liver.

2.2. Collection of data

In this study we analyzed the treatment response of DAA drugs among hepatitis C virus (HCV) patients with liver cirrhosis. Non-cirrhotic patients were also included as control cohort. The study included clinical data of patients treated at Shaikh Zayed Hospital Lahore, Pakistan between June 2018 to September 2020. Existing literature based on Pakistani population just examined the treatment response of interferon. Only 67% of HCV infected patients achieved SVR in response to interferon therapy and relapse rate was also very high. Because of increasing cases of treatment failure with interferon, treatment options were replaced with DAA drugs.

According to literature survey, the treatment protocol in HCV cirrhotic patients is sofosbuvir and velpatasvir (SOF + VEL) for 12 weeks and in non-cirrhotic patient are SOF + DCV for 12 weeks while we observed that both HCV cirrhotic and non-cirrhotic patients at Sheikh Zayed Hospital were prescribed sofosbuvir and daclatasvir (SOF + DCV) combination [11], possibly due to unavailability or less availability of protease inhibitors.

2.3. Inclusion and exclusion criteria

Our study included patients who had already completed their treatment during 2018 and 2020. Liver complications of patients was also taken into account to classify them according to staging of liver cirrhosis. Patients co-infected with HBV or other viral infections were excluded from the study.

2.4. Distribution and classification of data

Total 94 participants were recruited in the study. Patients were treated with DAA therapy (SOF + DCV) at Shaikh Zayed Hospital, Lahore. From June 2018 to September 2020, we collected the data from gastroenterology ward, OPD, and liver transplant (LT) ward of Shaikh Zayed Hospital. Forty-six patients were HCV cirrhotic out of 94 patients whereas 48 patients were HCV non-cirrhotic. We collected the information of all these patients through detailed interview and fill the questionnaire on the base of the laboratory tests and clinical parameters as well as collected the reports of LFTs, HCV RNA PCR and alpha-fetoprotein from participants. The patients were followed-up post-treatment to analyze the SVR rate in DAA drug treated HCV patients with cirrhotic and non-cirrhotic patients. Results of HCV PCR RNA were noticed pre-treatment, during the 1st month of treatment, 3rd month of treatment, at the completion of treatment, and 6-month post-treatment.

2.5. Analysis of data

After collection of data, it was distributed in two groups: HCV cirrhotic and non-cirrhotic patients. Out of 94 patients, 46 were cirrhotic and 48 were non-cirrhotic.

Means and standard deviations were calculated. The data analysis was done with the help of IBM SPSS version 21 software. Baseline

characteristics and clinical parameters were evaluated by using *t*-test. Age-wise and gender-wise treatment response between cirrhotic and non-cirrhotic patients was also analyzed using chi-square test. We also analyzed the prevalence of unusual case reports and co-morbid conditions in HCV cirrhotic and non-cirrhotic patients. P value less than 0.05 was considered statistically significant.

To determine the correlation between liver function test and alpha-fetoprotein we used Spearman's correlation test. The spearman's coefficient is denoted as Rho and results are displayed as positive or negative value. The positive sign show the direct relation and negative sign show indirect or inverse relation between two variables. The two variables show the different correlations in the form of weak, moderate and strong on the base of value of Rho. The analysis of entire dataset was accomplished by using the software of IBM SPSS version 21.

2.6. Ethical approval

Research Ethics and Support Committee (RESC 05/01/2020) of University of Management and Technology approved this study. Also, informed consent was obtained from all patients.

3. Results

Total 94 HCV positive patients infected with 3a genotype of HCV were enrolled in our study. All patients had received treatment with sofosbuvir and daclatasvir (SOF and DAC). Out of 46 cirrhotic patients, 38 were responders and 8 were non-responders to SOF + DCV combination. In the 48 patients with non-cirrhotic liver, 33 were responders and 15 were non-responders to DAA therapy. We observed the response rate was higher in cirrhotic patients as compared to non-cirrhotic patients because 82.60% of patients achieved sustained virological response (SVR) in HCV-infected cirrhotic patients and SVR rate in HCV infected non-cirrhotic patients was 68.75%. However, the difference in overall response rate between both study-groups was not significant ($p = 0.118$) (Fig. 1).

3.1. Demographics and biochemical parameters of HCV cirrhotic and non-cirrhotic patients

Our study confirmed that unsafe medical practices were the most common cause behind increasing risk of HCV because the virus holds the potential to spread among individuals through blood. The baseline characteristics and clinical parameters of HCV cirrhotic and non-cirrhotic patients are mentioned in Table 1. We analyzed the mean and standard deviation level of liver enzymes (ALP, ALT and AST), bilirubin, and creatinine. Liver function enzymes were found higher in cirrhotic patients as compared to non-cirrhotic while the level of albumin, total and direct bilirubin and creatinine were slightly higher in non-cirrhotic patients as compared to cirrhotic patients.

3.2. Gender-wise distribution in study groups

In our study, overall number of patients was 94. We analyzed that the prevalence of HCV between both study-groups and it higher in males (61; 64.89%) as compared to females (33; 35.10%). We did not find any significant difference ($p = 0.173$) between gender and

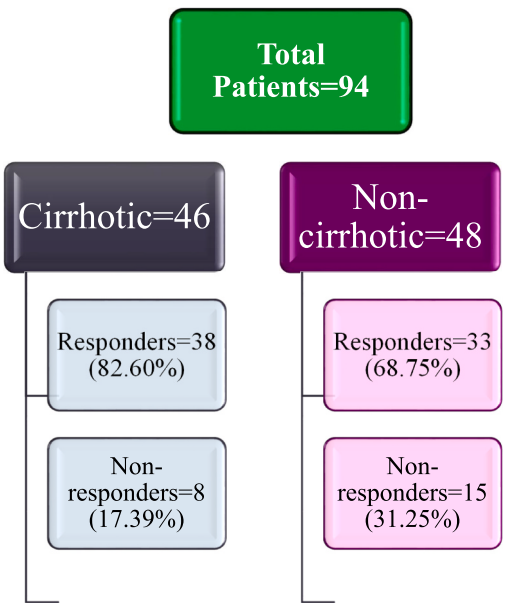


Fig. 1. Distribution of the participants of the study.

Table 1
Demographic characteristics and clinical parameters of HCV cirrhotic and non-cirrhotic patients.

Study Groups	Age	ALP	ALT	AST	Albumin	Total bilirubin	Direct bilirubin	Creatinine
Cirrhotic	56.28 ± 9.12	183.2 ± 107.7	66.82 ± 47.43	103.8 ± 72	2.59 ± 0.62	2.43 ± 3.43	1.27 ± 1.98	0.80 ± 0.35
Non-cirrhotic	46.96 ± 8.85	165.5 ± 160.06	35.14 ± 27.9	59.23 ± 43.2	2.66 ± 0.69	2.74 ± 3.98	1.29 ± 1.95	1.35 ± 1.70
p-value	0.173	0.065	0.013	0.025	0.68	0.12	0.678	0.565

liver-condition of HCV infected patients (Fig. 2).

3.3. Prevalence of HCV among different age groups

Overall findings of our study reported that most of the patients belonged to the middle age group of 40–60 years. Further age-wise distribution of study-participants showed that majority of patients in both cirrhotic and non-cirrhotic group were middle-aged.

We observed least prevalence of HCV cirrhotic patients in younger age group of 20–40 while, in HCV non-cirrhotic group least prevalence of participants was noticed in older age group i.e, >60 years (Fig. 3).

3.4. Response association towards treatment

We also analyzed the treatment response of DAA drugs in different age-groups and genders.

3.5. Association between gender and treatment response

Our findings reported that 46 patients were cirrhotic and 48 patients were non-cirrhotic, out of 94 hepatitis C patients. In 46 cirrhotic patients, 33 were males and 13 were females while in 48 non-cirrhotic patients, 28 were males and 20 were females. The findings of our study further confirmed that overall treatment response in both groups was better in female participants of our study as compared to male participants. However, that difference was not statistically significant in both cirrhotic study-group ($p = 0.822$) and non-cirrhotic study group ($p = 0.875$). Therefore, the response status of patients was independent of gender (Fig. 4).

3.6. Association between age and response

We observed the response rate of DAA drugs was found higher in the population of age group younger than 40 in HCV cirrhotic patients whereas in HCV non-cirrhotic patients, the response rate of DAA drugs was higher in the population of age group older than 40. Therefore, our study reported that DAA drugs are effective in all age group and the age wise treatment response in both gender was not statistically significant. We observed the number of responders was higher than non-responders in both younger and older age group. We did not found any significant difference ($p = 0.643$) between age and response of HCV cirrhotic patients as well as no significant difference ($p = 0.369$) between age and response of HCV non-cirrhotic patients. Hence, the response status of a patient is independent of age (Fig. 5).

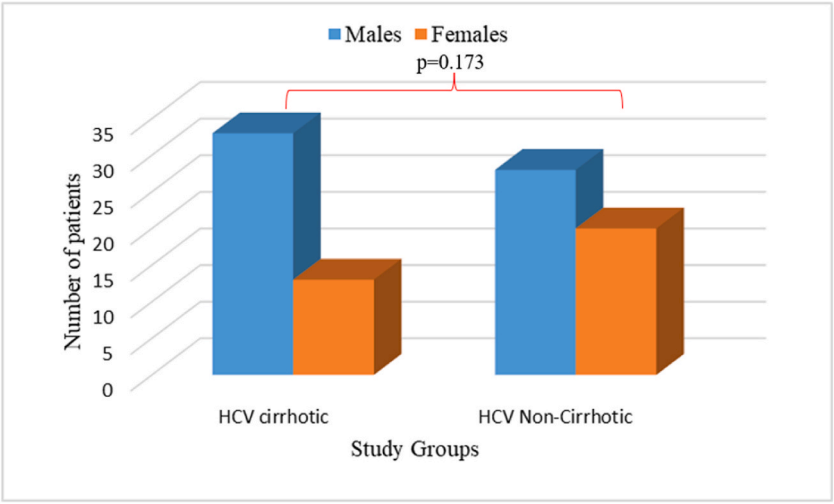


Fig. 2. Prevalence of HCV associated liver cirrhosis between genders.

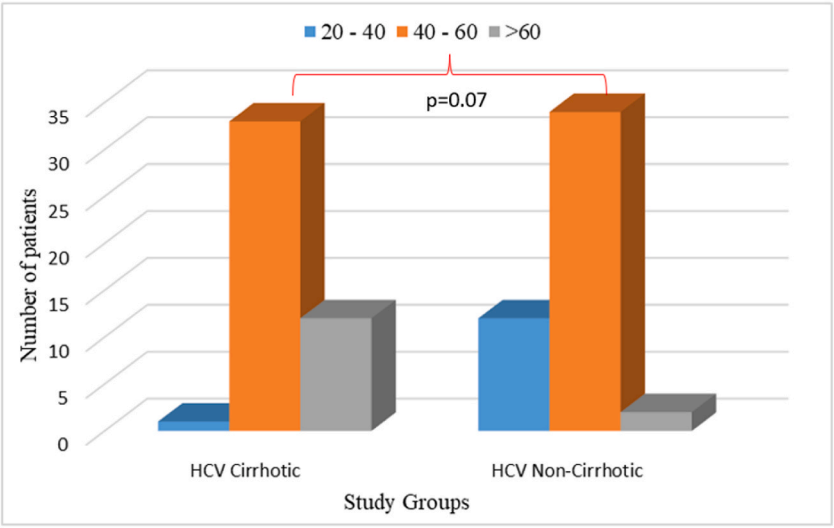


Fig. 3. Age - wise distribution in different HCV groups.

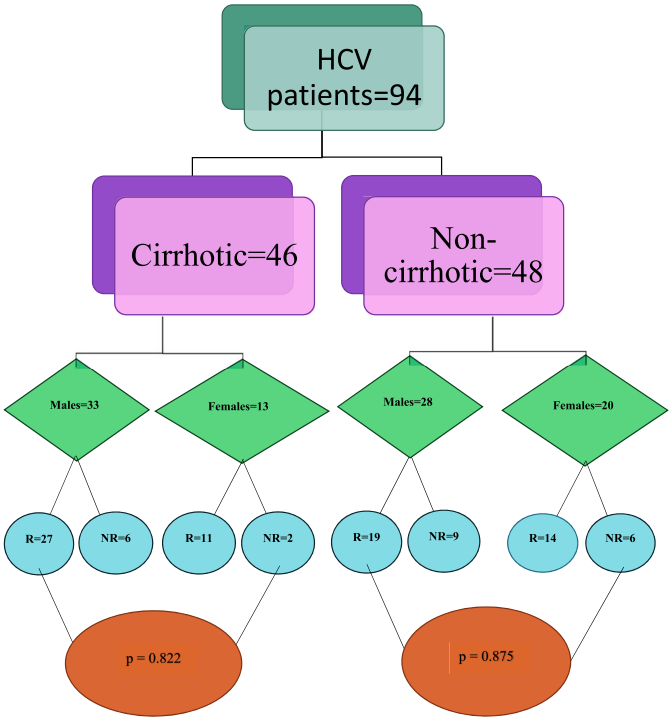


Fig. 4. Association between gender and response.

3.7. Prevalence of adverse effects in participants of study

Our study showed some adverse effects of DAAs in patients following the completion of treatment. Adverse outcomes observed in participants of our study include portosystemic encephalopathy (PSE), spontaneous bacterial peritonitis (SBP), hepatorenal syndrome (HRS), upper gastrointestinal bleeding (UGIB), hepatocellular carcinoma (HCC) and ascites during the follow up duration of therapy **(Table 2).** We observed the prevalence of HCC was high in HCV cirrhotic patients whereas the prevalence of ascites was high in HCV non-cirrhotic patients (Fig. 6).

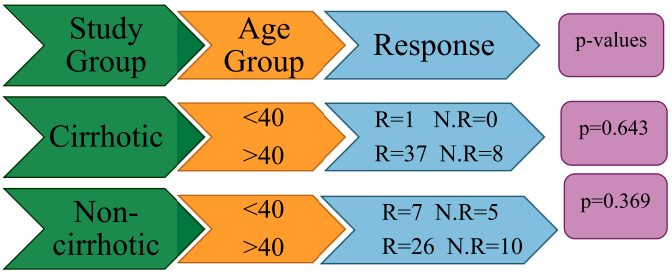


Fig. 5. Association between age and response.

Table 2
Adverse effects of DAAs in participants of study.

HCV patients	PSE	SBP	HRS	UGIB	HCC	Ascites
Cirrhotic	7 (30.43%)	2 (28.57%)	0	7 (43.75%)	44 (100%)	11 (30.55%)
Non-cirrhotic	16 (69.56%)	5 (71.42%)	4 (100%)	9 (56.25%)	0	25 (69.44%)
Total	23	7	4	16	44	36
p-value	NS	NS	0.05	NS	0.013	0.014

Portosystemic encephalopathy (PSE), Spontaneous bacterial peritonitis (SBP), Hepatorenal syndrome (HRS), Upper gastrointestinal bleeding (UGI), Hepatocellular carcinoma (HCC), non-significant (NS).

4. Prevalence of comorbid conditions in HCV groups

We observed some comorbid conditions including diabetes mellitus (DM), hypertension (HTN), splenomegaly, pancreatic exocrine insufficiency (PEI) and end stage liver disease (MELD) during the treatment with DAA drugs. Our findings showed that high prevalence of HTN in HCV cirrhotic patients whereas the high prevalence of DM in HCV non-cirrhotic patients (Fig. 7).

4.1. Relative association between LFTs and AFP

The findings of our study showed positive correlation of AFP with ALT, AST, ALP, albumin, and creatine (Fig. 8). The positive correlation of ALT and AST was found highly significant This finding indicates that the high value of AFP is the predictor of HCV patient to become HCV cirrhotic (Table 3).

5. Discussion

We studied the treatment response of direct acting antiviral drugs in HCV infected patients with liver cirrhosis. Previously, interferon was the standard of care therapy but it was replaced with DAA drugs because of high recurrence rate associated with

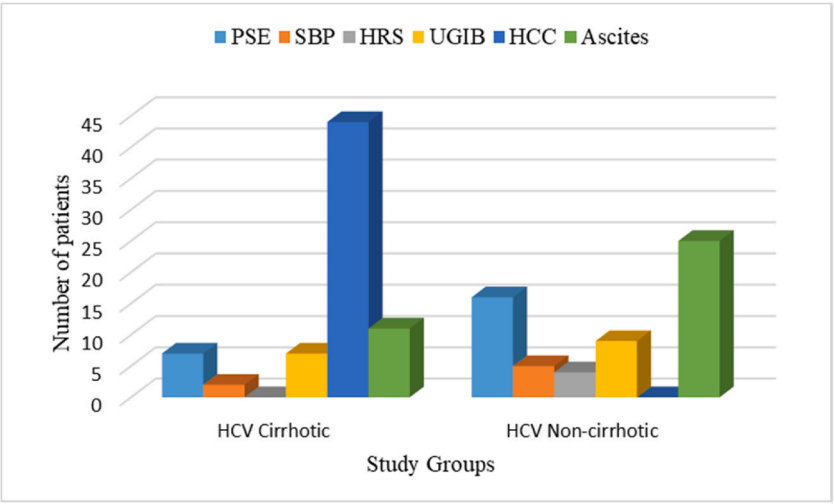


Fig. 6. Adverse effects in different study groups.

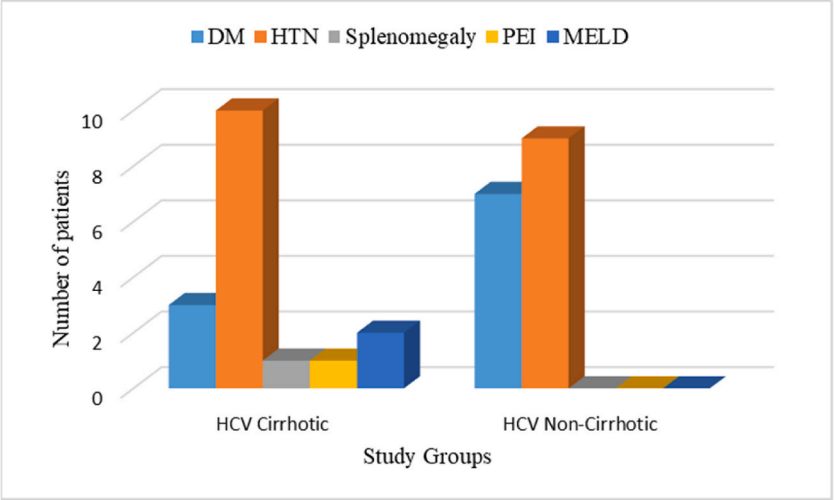


Fig. 7. Prevalence of comorbid conditions.

interferon. Some local resources have confirmed that interferon is still in use in Pakistan because of financial constraints and unavailability of cost-effective of DAA drugs. According to literature, interferon therapy is associated with low SVR rate. In contrast to which, development of DAA drugs turned out to be safe and efficacious treatment option against HCV. Despite of failure of interferon it is still being used in some low-income countries. This is the first study that analyzed the efficacy of DAA drugs in cirrhotic patients in Pakistan. This study further evaluated the correlation between LFTs and AFP.

Chronic HCV infection progresses to hepatocellular carcinoma (HCC) and then it becomes difficult to be treated. It is clear in several studies the treatment response after taking DAA drug combination (SOF + DCV) was good and effective in HCV infected cirrhotic patients [12]. Likewise, our study also confirmed that use of DAA drugs is equally safe in both cirrhotic and non-cirrhotic patients. The study also highlighted few adverse outcomes in minor proportion of study participants.

The response rate was equally safe and tolerable in patients of all age-groups in both cirrhotic and non-cirrhotic groups. Age-wise treatment response was not significantly different between both study-groups. In contrast to the findings of our study, Wahid B et al. (2018) reported poor SVR among older age (>60 years) patients as compared to patients of less than 60 years [13].

According to findings of our study, SVR rate was higher in females as compared to males following DAA drug therapy but this difference was not statistically significant. Therefore, our study confirmed that response rate of DAA drugs is independent of gender and age. In contrast to the findings of our study, Mushtaq et al. (2020) reported high response rates in male as compared to females [14]. We examined majority of patients in both study groups were in middle age group i.e 40-60. We also observed least prevalence of liver cirrhosis in HCV infected patients of younger age group of 20–40 years. According to Jhaveri et al. (2018) SVR rates and treatment response have been drastically improved with the development of DAA drugs as these drugs have high therapeutic potential and minimum side-effects. The study also clarified that DAAs are safe for patients of any age-group unlike interferon therapy that had poor response rate in elder patients due to comorbid conditions that are quite common in old-age [15].

We observed that SVR rate was 82.60% in cirrhotic patients 68.75% in non-cirrhotic patients. Recently, findings reported by Jain et al., reported high SVR rates in HCV cirrhotic patients towards DAA treatment [12]. A recently published study confirmed 94.4% SVR rate towards DAC + RBV + SOF combination in genotype 3 infected HCV patients (G3HCV) with decompensated or compensated cirrhosis [16]. Likewise, another study based on Georgian population analyzed the treatment response of sofosbuvir in G3HCV patients with advanced liver fibrosis. This study further indicated low rate of SVR in DCV/SOF treated group as compared to DCV/SOF/RBV treated group [17].

The liver inflammation, fibrosis and liver cirrhosis can also be caused by the higher level of liver enzymes (ALP, ALT and AST). This study also evaluated the LFTs with condition of liver in HCV patients. Ascites was the most common adverse effect faced by HCV infected non-cirrhotic patients while, in HCV cirrhotic patients, most common adverse outcome was HCC. Likewise, Desai et al., also revealed that high risk of HCC in HCV cirrhotic patients but this study noted that only 20% of HCC occur in non-cirrhotic patients [18]. A very recent study by Liu et al. (2020) investigated the predictors of and clinical outcome of DAA drugs and elevation of ALT during the course of treatment and reported elevation of ALT in 1/10th of chronic HCV patients with it has no impact on SVR following DAA drug therapy.

Several studies revealed chances of portal hypertension in HCV patients with cirrhotic liver but some studies discussed that hypertension also occur in non-cirrhotic liver named as non-cirrhotic portal hypertension. From our study, we found high prevalence of hypertension (52.6%) in HCV cirrhotic patients as compared to non-cirrhotic while the high prevalence of diabetes (70%) in non-cirrhotic as compared to cirrhotic patients. In contrast to our findings, this recent study demonstrated the high prevalence of diabetes mellitus in HCV cirrhotic patients [19].

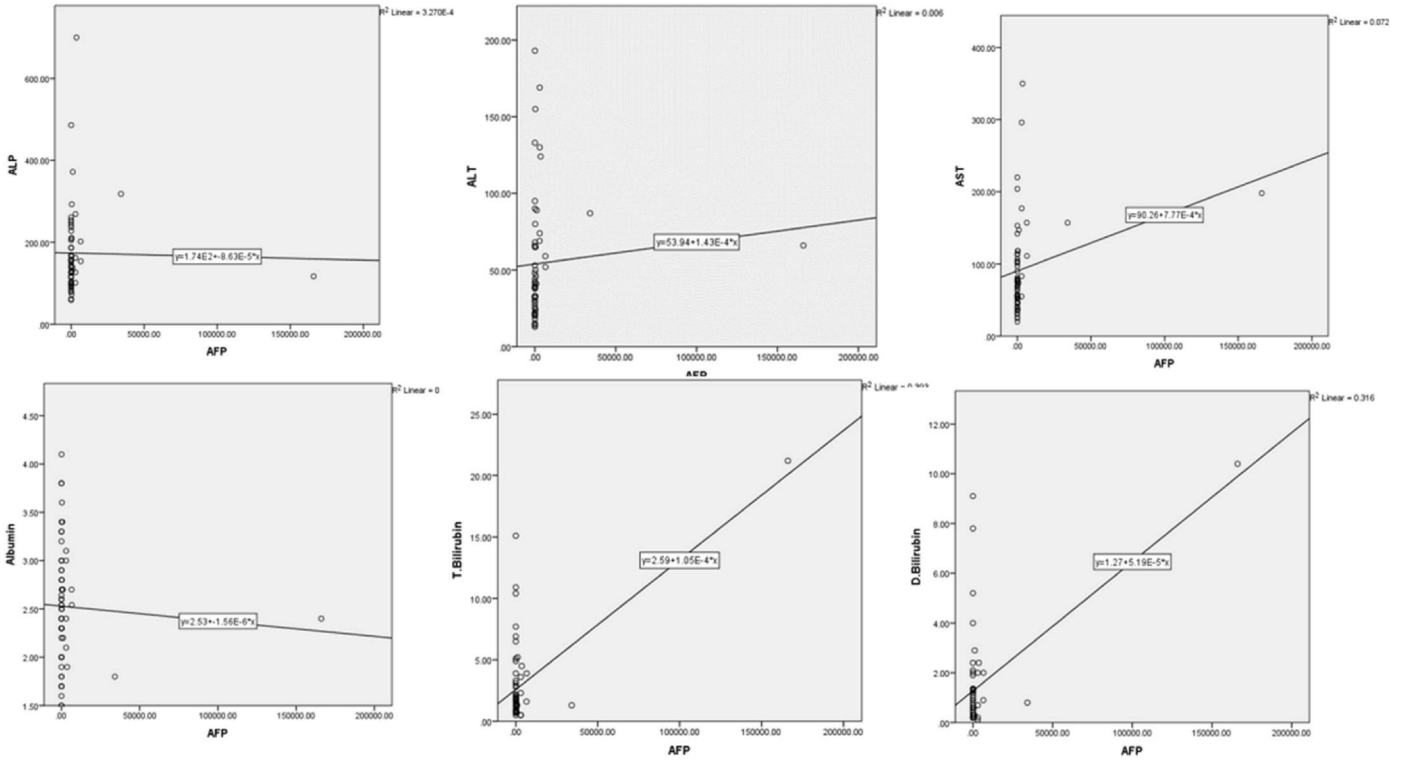


Fig. 8. Relative correlation of AFP with LFTs.

Table 3
Relative association of LFTs with AFP.

Parameters	Spearman's rho	p-value
ALP/AFP	0.252	0.061
ALT/AFP	0.524	0.000001
AST/AFP	0.497	0.000001
Albumin/AFP	0.220	0.103
Total Bilirubin/AFP	−0.11	0.421
Direct Bilirubin/AFP	−0.121	0.375
Creatinine/AFP	0.94	0.489

We observed the highly significant correlation between ALT and AFP as well as significant correlation between AST and AFP. Ali et al. (2019) also reported significant correlation between AST and AFP while no significant correlation between ALT and AFP [20].

6. Clinical significance

- Healthcare practitioners need to optimize treatment regimens against HCV cirrhotic and non-cirrhotic patients.
- Our study highlighted the need to strictly follow international and national treatment guidelines
- Further studies are needed to find out the correlation of DAA drugs with adverse outcomes observed post-treatment, in Pakistani population.
- Regular monitoring of tests such as AFP test, endoscopy and LFTs post treatment so that DAA drug induced adverse outcomes can be detected at early stages.
- Financial cost is a huge barrier. Government officials must ensure the easy and cost-effective availability of all classes of DAA drugs in Pakistan.

7. Conclusion

According to findings of our study, 82.60% of HCV cirrhotic patients achieved SVR and while, SVR rate among HCV non-cirrhotic patients was 68.75%. Our study further confirmed that second generation interferon-free regimens are highly effective in both study groups. The study further confirmed that treatment response was independent of gender and age. In our study the liver function test, viral load and AFP were the predictors of response rate. DAA drugs are overall well-tolerated and safe. We also observed some adverse effects among patients treated with interferon-free regimens.

Author contribution statement

Hafiza Arooba Riaz: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.
Dure Nishwa: Performed the experiments, Analyzed and interpreted the data.
Ameer Fatima: Analyzed and interpreted the data.
Braira WAHID: Conceived and designed the experiments; Wrote the paper.
Babita Kumari: Contributed reagents, materials, analysis tools or data.
Muhammad Idrees: Contributed reagents, materials, analysis tools or data.

Data availability statement

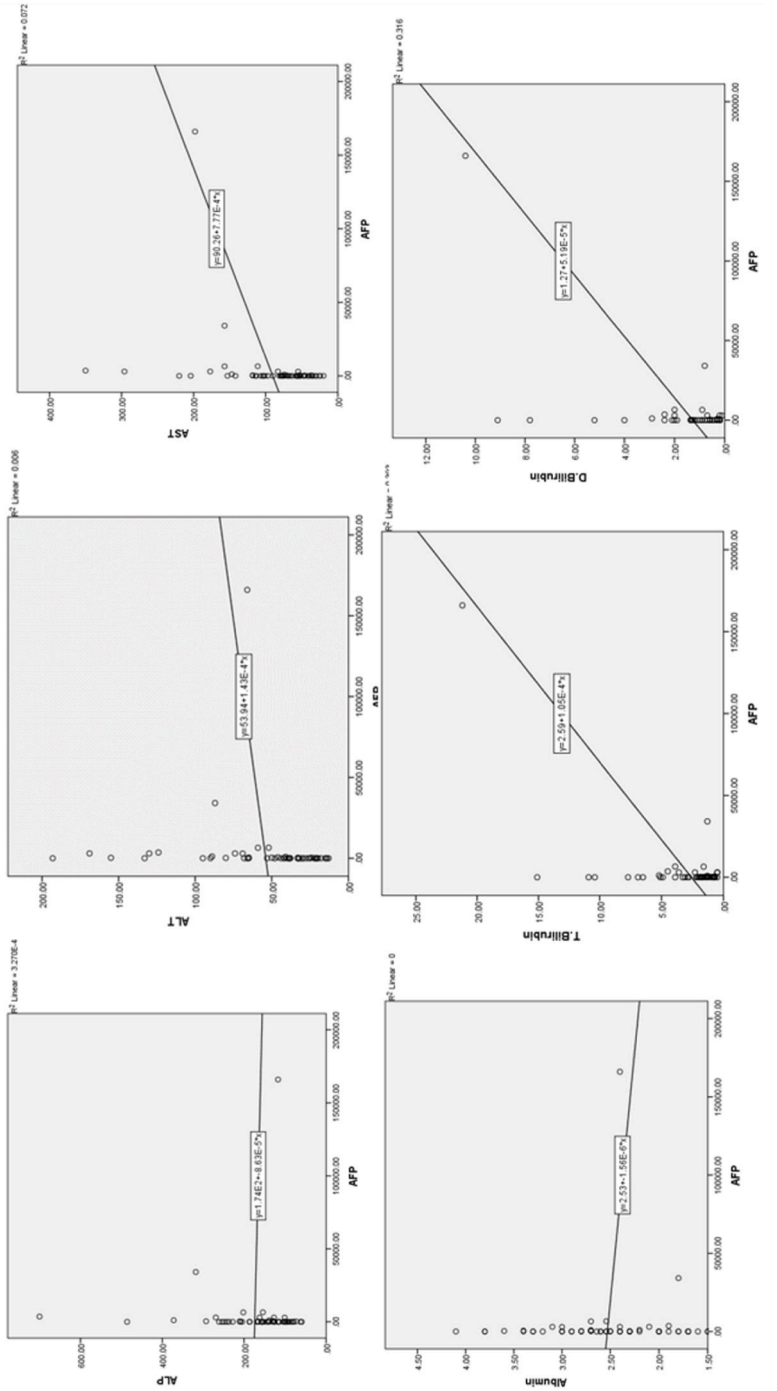
Data will be made available on request.

Funding

None.

Contribution of authors

BW and MI conceived and designed the experiments; HAR, DN, and AF, performed the experiments; HAR, DN, and BW, BK analyzed and interpreted the data; BW, MI and AA contributed reagents, materials, analysis tools or data; BW and HAR wrote the paper.


AST
AFP
y=60.26+1.77E-4*x
R² Linear = 0.072
D.Billirubin
AFP
y=1.37+5.19E-5*x
R² Linear = 0.316
ALT
AFP
y=53.94+1.43E-4*x
R² Linear = 0.006
T.Billirubin
AFP
y=2.59+1.05E-4*x
ALP
AFP
y=1.74E2+-8.63E-5*x
R² Linear = 3.270E-4
Albumin
AFP
y=2.53+-1.56E-6*x
R² Linear = 0

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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